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ORIGINAL REPORT

Vincristine, Actinomycin, and Cyclophosphamide Compared With Vincristine, Actinomycin, and Cyclophosphamide Alternating With Vincristine, Topotecan, and Cyclophosphamide for Intermediate-Risk Rhabdomyosarcoma: Children's Oncology Group Study D9803

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ABSTRACT

Purpose
The purpose of this study was to compare the outcome of patients with intermediate-risk rhabdomyosarcoma (RMS) treated with standard VAC (vincristine, dactinomycin, and cyclophosphamide) chemotherapy to that of patients treated with VAC alternating with vincristine, topotecan, and cyclophosphamide (VAC/VTC).

Patients and Methods
Patients were randomly assigned to 39 weeks of VAC versus VAC/VTC; local therapy began after week 12. Patients with parameningeal RMS with intracranial extension (PME) were treated with VAC and immediate x-ray therapy. The primary study end point was failure-free survival (FFS). The study was designed with 80% power (5% two-sided α level) to detect an increase in 5-year FFS from 64% to 75% with VAC/VTC.

Results
A total of 617 eligible patients were entered onto the study: 264 were randomly assigned to VAC and 252 to VAC/VTC; 101 PME patients were nonrandomly treated with VAC. Treatment strata were embryonal RMS, stage 2/3, group III (33%); embryonal RMS, group IV, less than age 10 years (7%); alveolar RMS or undifferentiated sarcoma (UDS), stage 1 or group I (17%); alveolar RMS/UDS (27%); and PME (16%). At a median follow-up of 4.3 years, 4-year FFS was 73% with VAC and 68% with VAC/VTC ($P = .3$). There was no difference in effect of VAC versus VAC/VTC across risk groups. The frequency of second malignancies was similar between the two treatment groups.

Conclusion
For intermediate-risk RMS, VAC/VTC does not significantly improve FFS compared with VAC.

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INTRODUCTION

Cure rates for rhabdomyosarcoma (RMS) have increased from 25% in the 1970s to 70% in 1990s.[1-3] During this time, the Intergroup Rhabdomyosarcoma Study (IRS) Group conducted four consecutive trials.[4-7] Multimodal therapy, including combination chemotherapy, surgery, and/or radiation therapy (RT) in the majority of patients, has become standard for RMS. IRS-IV failed to show improvement in outcome for patients with nonmetastatic disease when ifosfamide was substituted for cyclophosphamide, or when etoposide and ifosfamide were substituted for dactinomycin and cyclophosphamide, respectively.[7] Therefore, vincristine, dactinomycin, and cyclophosphamide (VAC) remained the standard chemotherapy in North America for nonmetastatic RMS.

Despite the improvement in outcome for RMS, cure rates for patients with embryonal RMS with gross disease at unfavorable sites and all nonmetastatic alveolar RMS (together classified as "intermediate-risk disease") continue to be suboptimal (5-year failure-free survival [FFS], 65%). This intermediate-risk group did not have improved outcome on IRS-IV compared with IRS-III, thus not benefitting from the increased dose of the alkylating agent on IRS-IV compared with the dose on

IRS-III.[8] A subsequent pilot study with further cyclophosphamide dose intensification during induction did not result in improved outcome.[9]

Topotecan, a topoisomerase I inhibitor, showed significant activity both alone and in combination with cyclophosphamide in newly diagnosed stage 4 patients (46% and 47% response rates, respectively), and topotecan combined with cyclophosphamide was active in recurrent RMS.[10-13] These findings suggested that the combination of topotecan and cyclophosphamide were promising enough to evaluate in a randomized clinical trial. The primary aim of this trial was to compare the outcome of patients with intermediate-risk RMS treated with standard VAC chemotherapy to that of patients treated with VAC alternating with vincristine, topotecan, and cyclophosphamide (VAC/VTC). The hypothesis was that substitution of topotecan for dactinomycin in approximately half the treatment cycles would improve the outcome of patients with intermediate-risk RMS. A secondary objective was to determine the rate of local failure in selected patients with group III tumors who, following second-look surgery, had response-adjusted radiotherapy (the subject of a separate analysis).

PATIENTS AND METHODS

Eligibility/Patient Classification

Intermediate-risk RMS was defined as stages 2 and 3, clinical group III embryonal (including botryoid and spindle cell) RMS, and all nonmetastatic alveolar (defined as any part of the tumor having an alveolar component) RMS, undifferentiated sarcoma (UDS), or ectomesenchymoma. Previous analysis suggested that patients with stage 4, clinical group IV embryonal RMS who were younger than age 10 had an outcome similar to the intermediate-risk group; therefore, this subgroup of patients was also included.[14] Tissue submission for central review of tumor material was required to confirm histology and study eligibility. Central review pathology diagnosis (when available) was used in the statistical analysis. Informed consent was obtained from patients, their parents, or both, according to guidelines of the National Cancer Institute (NCI). Eligibility criteria were as follows: previously untreated patients younger than age 50, beginning of therapy within 42 days after initial biopsy, serum bilirubin of $\leq$ 1.5 mg/dL, and normal serum creatinine for age (with the exception of elevated creatinine secondary to tumor obstruction).

Imaging studies and surgical findings determined the extent of disease. Patients were assigned to a clinical group by each participating institution following surgery on the basis of clinicopathologic determination of extent of

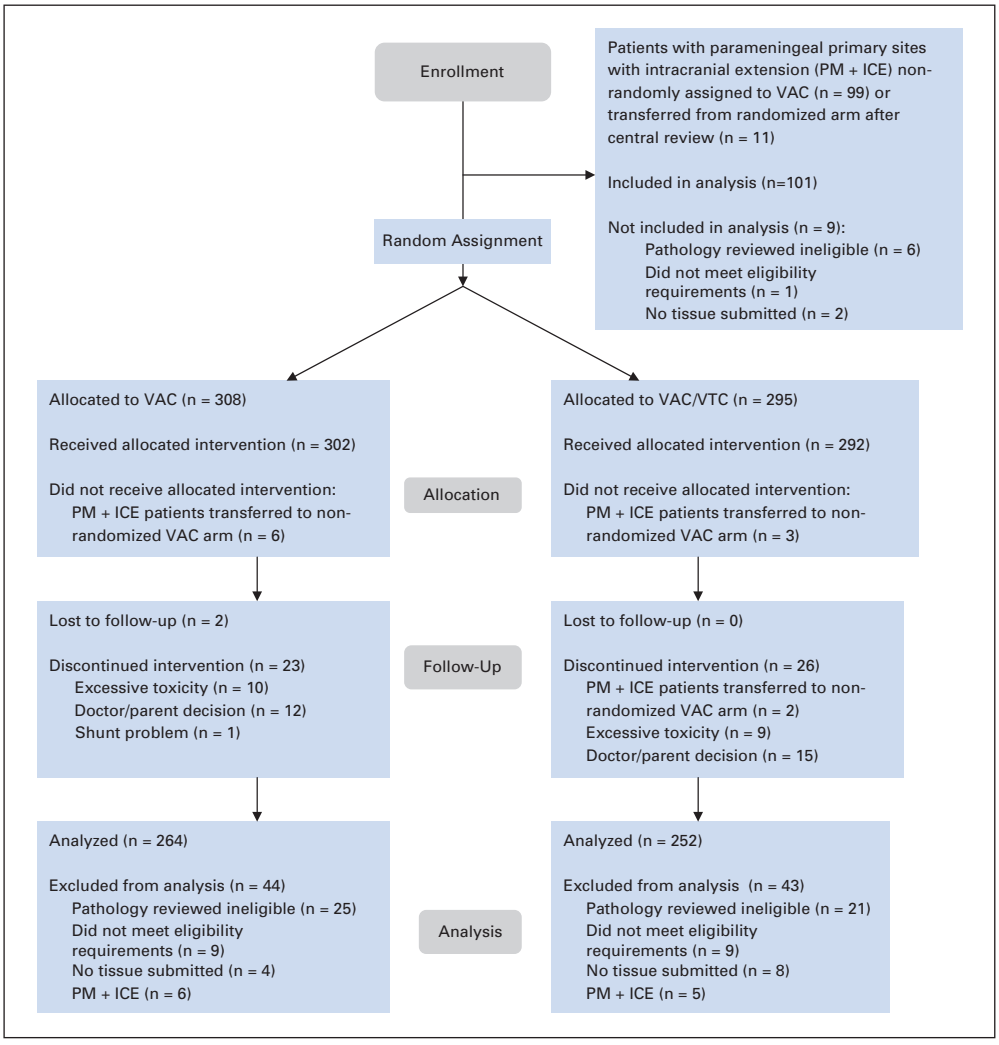

Fig 1. CONSORT diagram. VAC, vincristine, dactinomycin, and cyclophosphamide; VAC/VTC, VAC alternating with vincristine, topotecan, and cyclophosphamide; PM + ICE, parameneogeal rhabdomyosarcoma with intracranial extension.

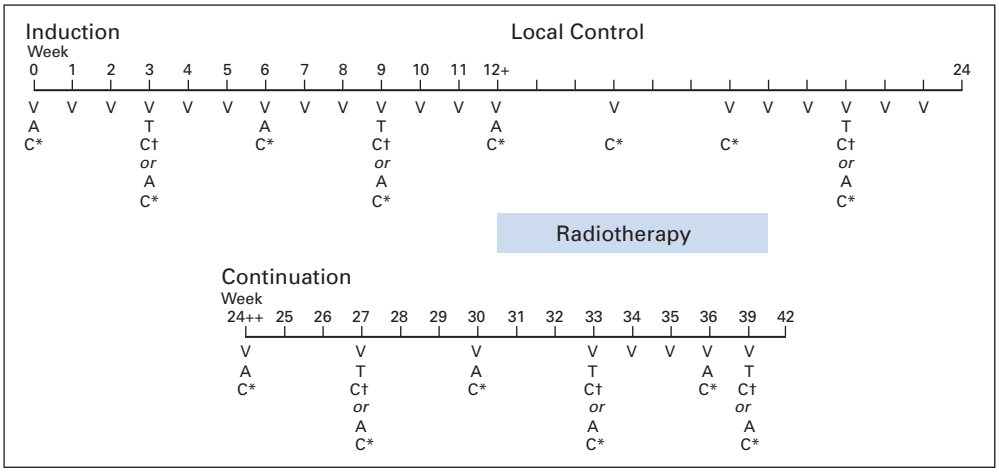

Fig 2. Treatment schema: randomized schedule of either vincristine, dactinomycin, and cyclophosphamide (VAC) or VAC alternating with vincristine, topotecan, and cyclophosphamide (VAC/VTC) at weeks 3, 9, 21, 27, 33, and 39. Doses of drugs for children age 3 years and older were vincristine (V) 1.5 mg/m^2 (top dose, 2 mg) × 1 day; dactinomycin (A) 0.045 mg/kg × 1 day (maximum dose, 2.5 mg); topotecan (T) 0.75 mg/m^2 × 5 days; cyclophosphamide (C*) 2.2 g/m^2 × 1 dose (with mesna uroprotection); cyclophosphamide (C†) 250 mg/m^2/dose for 5 days.

disease and degree of surgical resection, according to criteria of the IRS Postsurgical Grouping Classification.[3] If primary re-excision of tumor was the definitive operation, patients were classified according to clinical group after this operation, provided it was performed within 42 days of the initial procedure and before beginning protocol-specified chemotherapy. Appropriate lymph node sampling, based on primary site of disease, was required for paratesticular RMS in boys older than age 10 and in patients with extremity tumors, and was recommended for clinically positive nodes (large lymph node size or abnormal imaging studies) before study enrollment. Patients were also assigned a presurgical stage on the basis of tumor site, tumor size, presence or absence of clinically involved lymph nodes, and/or metastatic disease.[3] Stage and group were reviewed by a surgical review committee and, when available, used in outcomes analysis (Fig 1).

Chemotherapy

Patients were randomly assigned to one of two treatment regimens: VAC or VAC/VTC. Patients with parameningeal primary tumors with intracranial extension (PME), defined as any imaging evidence that the primary tumor touched, displaced, invaded, distorted, or otherwise caused a signal abnormality of the dura in contiguity to the primary tumor site, were assigned to treatment with VAC and immediate RT (nonrandomized VAC). Treatment schemas are shown in Figure 2. Dose modifications (previously reported) were instituted in 2002 for children younger than age 3 at time of treatment because of an excessive rate of hepatopathy and death from hepatic veno-occlusive disease in this age group.[15] Doses by age are listed in Table 1.

Primary Tumor Treatment

Patients were evaluated for response at weeks 12, 24, and end of therapy. If at week 12 excision of the tumor with negative margins in group III patients was feasible, with organ preservation and without loss of form or function, this was encouraged and the radiation dose was adjusted according to the amount of residual tumor. Selected patients who responded poorly to induction chemotherapy were recommended to proceed to preoperative RT followed by second-look surgery at week 24.

Patients received response-adjusted RT according to stage, group, and histologic subtype at diagnosis and disease status after second-look surgery (if done) at week 12. Patients who at diagnosis had group I and group II N0 alveolar or undifferentiated tumors received 36 Gy, and group II N1 patients received 41.4 Gy at week 12. The dose of radiotherapy for patients with group III tumors varied according to results of resection. Patients received 36 Gy if the tumor was completely resected with negative margins at week 12. Patients with microscopic residual tumor after resection at week 12, or patients in clinical complete remission by imaging criteria with biopsy confirmation received 41.4 Gy. All other group III patients received 50.4 Gy. Dactinomycin and topotecan were withheld during RT. RT began 2 to 3 days after completion of week 12 chemotherapy if no biopsy or second-look operation was done, or 2 to 3 weeks after surgery for patients who underwent second-look surgery. Patients with PME began RT at week 1, as soon as possible after completion of the first VAC chemotherapy.

RT was delivered using megavoltage photon and/or electron beams. Brachytherapy was permitted in select patients. The recommended irradiated volume was the presurgical and prechemotherapy disease extent plus 1.5 to 2 cm. Volume reduction was permitted for patients whose total dose was 50.4 Gy. The initial planning volume was reduced to the original gross tumor volume plus 5 mm after a tumor dose of 36 Gy (if node-negative) or 41.4 Gy (if node-positive).

Definition of End Points

FFS was defined as time from therapy initiation to disease progression, recurrence, or death from any cause, and overall survival (OS) was time from therapy initiation to death from any cause. FFS and OS were censored at the patient's last contact date.

Statistical Methods

The primary comparison was between the two randomized regimens. Patients with PME who were not randomly assigned were compared with similar IRS-IV patients. Patients were stratified before random assignment into five strata: embryonal RMS, stage 2 or 3, group III; embryonal RMS, group IV, younger than age 10; alveolar RMS or UDS, stage 1 or group I; alveolar RMS or UDS, stage 2 or 3, group II/III; and PME stage 2 or 3.

Long-term FFS was expected to be 64%, on the basis of IRS-III and IRS-IV.[6,7] The study was designed with 80% power (two-sided α level of .05) to

Table 1. Chemotherapy Doses by Age for Vincristine, Dactinomycin, and Cyclophosphamide

Age (years)	Vincristine	Dactinomycin (mg/kg)	Cyclophosphamide + Actinomycin	Topotecan (mg/m^2/d × 5)	Cyclophosphamide + Topotecan (mg/m^2/d × 5)
< 1	0.025 mg/kg	0.025	36 mg/kg	0.75	250
1-3	0.05 mg/kg	0.045	73 mg/kg	0.75	250
> 3	1.5 mg/m^2	0.045	2,200 mg/m^2	0.75	250

detect an overall increase in the 5-year FFS from 64% with VAC to 75% with VAC/VTC. A total of 158 failures were required, which was projected to occur after the enrollment and follow-up of 518 patients.

FFS and OS rates were estimated using the Kaplan-Meier method[16] and compared between groups using the log-rank test.[17] Cox proportional hazards regression modeling was used to estimate hazard ratios and to investigate whether the effect of VAC/VTC versus VAC differed by risk stratum by including in the model a treatment effect, a categorical risk group effect, and the interaction between treatment and risk group.[18] A χ^2 test was used to compare toxicity rates over the treatment period.

The study was monitored by a data and safety monitoring committee, and three formal interim analyses of FFS were conducted. An O'Brien-Fleming boundary was used for the efficacy boundary. The Harrington-Fleming-O'Brien process of repeated testing of the alternative hypothesis at an α level of .005 was used for futility monitoring. The final α level for this fourth analysis was .043.[19] Local, regional, and distant failure rates were estimated using cumulative incidence curves. Follow-up was current through June 30, 2008. The median follow-up was 4.3 years (range, 0 to 8.2 years).

RESULTS

Patient Population

Between September 1, 1999, and August 5, 2005, 702 patients were enrolled. Eighty-five (12%) were ineligible for analysis. Of the remaining 617 eligible patients included in the analysis, 516 were randomly assigned to either VAC (n = 264) or VAC/VTC (n = 252), with the remaining 101 patients with PME primaries nonrandomly treated with VAC (CONSORT diagram; Fig 1).

Patient or Tumor Characteristics

Table 2 shows presenting characteristics of eligible patients. Histopathologic classification of tumors, according to the IRS Pathology Review Committee, was used to determine eligibility. Review Committee data are available for 484 cases (78% of 617 eligible patients). The concordance rate between central review and institutional diagnosis was 96% for patients with an institutional alveolar diagnosis and 85% for patients with an institutional embryonal/spindle cell/botryoid diagnosis. Twenty-seven patients were missing institutional pathology information of whom 22 had a central review alveolar/UDS diagnosis and five had a central review embryonal/spindle cell/botryoid diagnosis. Using central pathology review diagnosis, there were 219 embryonal tumors, 240 alveolar tumors, and 25 tumors with RMS not otherwise specified.

Group classification based on institutional data was available for 584 patients. Among these, group classification based on surgical review data was available for 565 patients. Concordance of institutional and central review committee group assignment was seen in 75% of group I, 73% of group II, and 97% of group III and IV patients.

Chemotherapy Doses Administered

The percentage of courses in which therapy was administered as recommended by protocol was 89% or greater for each regimen group across all phases and courses of therapy and did not differ by treatment regimen.

Treatment Outcome: Randomized Comparison

The estimated 4-year FFS rates were 73% for VAC and 68% for VAC/VTC, which do not differ significantly ($P = .3$; Fig 3A). The 4-year FFS for similar patients treated on IRS-IV was 69%. The relative hazard rate associated with VAC/VTC therapy versus VAC therapy was 1.19 (95% CI, 0.85 to 1.66). Estimated OS at 4 years was 79% for VAC and VAC/VTC (log-rank test, $P = .9$; Fig 3B). In comparison, the 4-year OS for similar patients treated on IRS-IV was 77%.

There was no difference in effect of VAC versus VAC/VTC across risk groups (test of interaction, $P = .3$). As an exploratory analysis, when FFS was analyzed by treatment stratum, there was a slightly higher risk of failure among patients with stage 2/3 or group II/III alveolar RMS or UDS who were treated with VAC/VTC compared with VAC alone ($P = .05$), while differences within other strata were not significant (Table 3).

Treatment Outcome: PME

Four-year FFS and OS for patients with PME who were nonrandomly assigned to VAC (n = 101) were 68% and 71%, respectively, compared with 61% FFS and 65% OS for similar patients treated on IRS-IV (n = 87). The FFS and OS distributions do not differ significantly between patients on IRS-IV and this study's patients with PME ($P = .4$ and $P = .4$, respectively).

Outcome by Risk Group Stratum

FFS distributions differed significantly among risk group strata when treatment arms were combined ($P = .001$, Fig 4). Four-year FFS rates were 83% for alveolar/UDS stage 1 or group I patients (*v* 74% on IRS-IV); 74% for embryonal, stage 2/3, group III patients (77% on IRS-IV); 68% for PME patients (62% on IRS-IV); 60% for alveolar/UDS stage 2/3 and group II/III patients (57% on IRS-IV), and 59% for patients younger than age 10 years with embryonal group IV disease (36% on IRS-IV).

Details of Treatment Failure

With a median follow-up of 4.3 years, there were 177 treatment failures. Across all therapy groups, 166 patients relapsed; seven patients died from infection, myelodysplastic syndrome, or pulmonary fibrosis without a prior event; and four patients died from complications of veno-occlusive disease without a prior event. The 4-year local failure rate, defined as any recurrence at the site of primary disease with or without recurrence involving a regional node or metastatic site, was 16.5% on VAC and 18.5% on VAC/VTC ($P = .5$). The 4-year regional failure rates involving regional lymph nodes with or without local or distant recurrence were 4.5% and 4.8% on VAC and VAC/VTC, respectively ($P = .9$). The 4-year distant failure rate, involving any metastatic disease, was 10.5% for VAC and 13% for VAC/VTC ($P = .4$). The impact of second-look surgery on local failure and RT dose reduction will be the subject of a separate analysis.

Toxicity

The worst degree of toxicity (hematologic and nonhematologic toxicity using NCI toxicity scoring criteria) during each phase and course of treatment was recorded for each patient. The most common grade 3 or 4 toxicities, summarizing across all phases and courses of therapy and presented as the rate for VAC versus VAC/VTC patients, were febrile neutropenia (85%, 78%), anemia (55%, 58%), clinically documented infection (54%, 55%), leukopenia (60%, 62%), lymphopenia (22%, 26%), neutropenia (63%, 65%), and thrombocytopenia (51%, 53%). Patients on VAC were more likely to develop febrile neutropenia ($P = .04$) but no other differences were statistically

Table 2. Baseline Characteristics of 617 Eligible Patients Enrolled on COG D9803

Baseline Characteristic	Treatment Assignment: Randomized VAC (n = 264) Count	%	Randomized VAC/VTC (n = 252) Count	%	Nonrandomized VAC (n = 101) Count	%
Sex						
Male	167	63	167	66	54	53
Female	97	37	85	34	47	47
Age, years						
< 1	12	5	5	2	1	1
1-9	184	70	173	69	68	67
10+	68	26	74	29	32	32
Race/ethnicity						
White	177	67	170	67	70	69
Black	35	13	31	12	15	15
Hispanic	30	11	30	12	14	14
Other	22	8	21	8	2	2
Histology (composite)						
Embryonal	119	46	106	43	62	62
Alveolar	122	47	126	51	30	30
UDS	11	4	5	2	1	1
RMS, NOS	9	3	12	5	7	7
Tumor size (composite)						
≤ 5 cm	99	39	108	44	41	41
> 5 cm	158	61	139	56	59	59
Primary site (composite)						
Extremity	45	18	46	19	0	
GU/BP	47	18	48	19	0	
Parameningeal	57	22	58	23	99	99
Retroperitoneal/perineal	50	19	35	14	0	
Other	58	23	62	25	1	1
Tumor stage (composite)						
1	38	15	46	18	0	
2	60	23	63	25	34	34
3	140	54	121	48	59	59
4	19	7	20	8	7	7
Group (composite)						
I	20	8	12	5	0	
II	34	13	42	17	1	1
III	184	72	175	70	92	92
IV	19	7	21	8	7	7
Regional lymph nodes (composite)						
N0	217	82	196	78	79	78
N1	40	15	53	21	21	21
NX	7	3	3	1	1	1
Tumor invasion (composite)						
T1	136	53	127	51	17	17
T2	120	47	121	49	83	83

NOTE. The percentage values are calculated within each column among patients with nonmissing data. Composite variables reflect central review data if available; otherwise, the value reported by the institution was used.

Abbreviations: COG, Children's Oncology Group; VAC, vincristine, dactinomycin, and cyclophosphamide; VAC/VTC, VAC alternating with vincristine, topotecan, and cyclophosphamide; UDS, undifferentiated sarcoma; RMS, rhabdomyosarcoma; NOS, not otherwise specified; GU, genitourinary; BP, bladder and prostate.

significant. Seventeen (2.8%) of the 617 eligible subjects had evidence of severe hepatopathy (previously reported[15]), similar to the 3.1% incidence for VAC on IRS-IV.[20]

There were 17 second malignancies (SMN), six on VAC/VTC, nine on randomized VAC and two on nonrandomized VAC. Seven were hematologic and 10 were solid tumors (four in the radiation field). Fifteen of the 17 patients had received RT. There was no significant difference between the randomly assigned VAC and VAC/VTC patients in the risk of SMN ($P = .6$).

DISCUSSION

Topotecan with and without cyclophosphamide was shown to be active in RMS in preclinical studies, as well as phase II relapse and up-front window studies. Trial authors hypothesized that the outcome for patients with intermediate-risk RMS would be improved by substituting topotecan/cyclophosphamide for half the cycles of dactinomycin/cyclophosphamide compared with that in patients

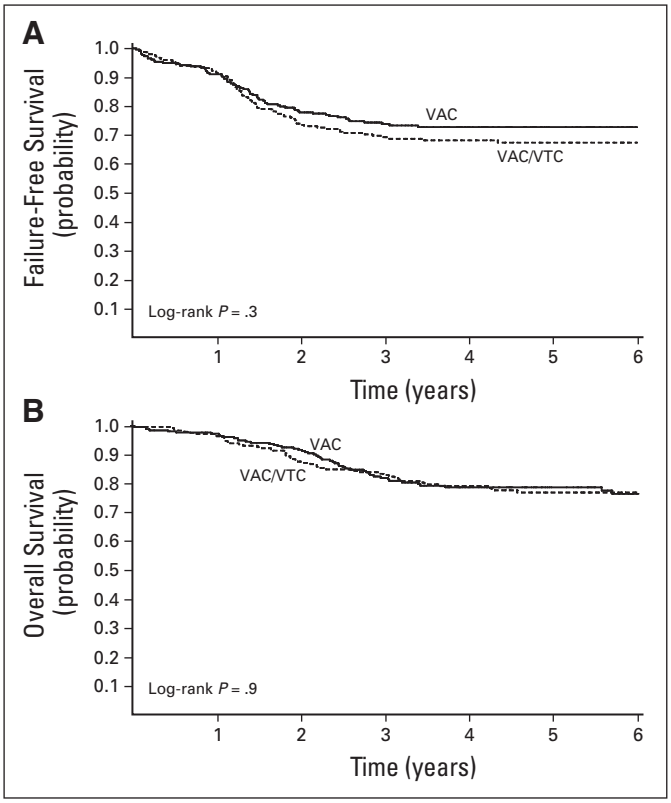

Fig 3. Outcome by treatment regimen. (A) Failure-free survival; (B) overall survival. VAC, vincristine, dactinomycin, and cyclophosphamide; VAC/VTC, VAC alternating with vincristine, topotecan, and cyclophosphamide.

treated with VAC alone, using a study design similar to that used by Grier et al[21] in which a promising drug pair (ifosfamide/etoposide) was alternated with standard therapy for Ewing's sarcoma. However, the 4-year OS and FFS remained unchanged from that in IRS-IV, irrespective of treatment regimen. Patterns of recurrence did not differ by treatment regimen.

The only toxicity difference between the two regimens was a higher incidence of febrile neutropenia seen with VAC. The percent of chemotherapy doses administered per protocol, including protocol-specified modifications for toxicity, were similar between randomized treatment regimens.

Table 3. Outcome by Treatment Stratum and Regimen

Treatment Stratum	4-Year FFS				
	VAC		VAC/VTC		
	No.	%	No.	%	P*
ERMS, stage 2/3, group III	106	76	99	73	.7
ERMS, group IV, < age 10 years	19	64	18	56	.6
ARMS/UDS, stage 1 or group I	51	77	55	88	.3
ARMS/UDS, stage 2/3, group II/III	88	68	80	52	.05
PM with ICE	101	68			

Abbreviations: FFS, failure-free survival; VAC, vincristine, dactinomycin, and cyclophosphamide; VAC/VTC, VAC alternating with vincristine, topotecan, and cyclophosphamide; ERMS, embryonal rhabdomyosarcoma; ARMS, alveolar rhabdomyosarcoma; UDS, undifferentiated sarcoma; PM with ICE, parameningeal rhabdomyosarcoma with intracranial extension.
*Log-rank test.

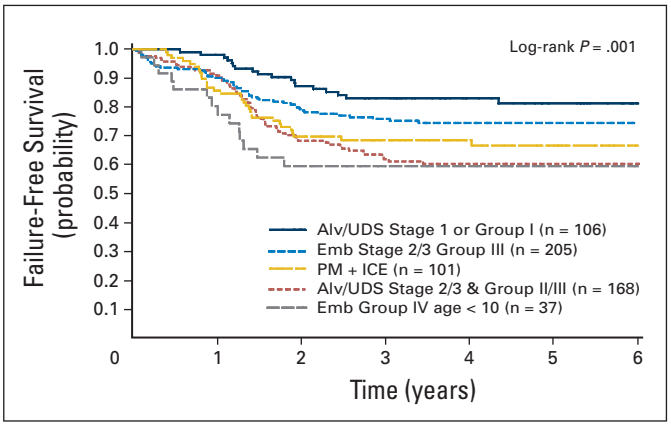

Fig 4. Failure-free survival by risk group stratum (all therapy groups combined). Alv, alveolar; UDS, undifferentiated sarcoma; Emb, embryonal; PM + ICE, parameningeal rhabdomyosarcoma with intracranial extension.

The total dose of cyclophosphamide on the VAC regimen of this study was 30.8 g/m^2 compared with 25.1 g/m^2 on the VAC/VTC regimen, giving the VAC/VTC regimen 20% less cyclophosphamide. Despite the lower total cyclophosphamide dose on the VAC/VTC regimen, the outcome of patients was similar to that on IRS-IV and on the VAC regimen of this study. This is not surprising, given that patients with unresectable tumors at unfavorable sites did not benefit from intensified cyclophosphamide therapy on IRS-IV compared with IRS-III.[8] The current series of RMS studies uses a dose of 1.2 g/m^2/course cyclophosphamide for all patients.

In preliminary phase II window trials of topotecan alone and with cyclophosphamide, there was a trend (not statistically significant) toward higher response rate for alveolar than for embryonal histology.[10,11] While Children's Oncology Group (COG) D9803 was not designed to compare outcome by histology, patients with alveolar histology were at increased risk of failure compared with those with embryonal histology and did not seem to benefit from VTC (Table 3).

This study has confirmed previous reports of increased failure risk with increased stage and group and in patients with alveolar compared with those with embryonal histology. This is similar to IRS-IV, which also had worse outcome for patients with alveolar subtype.[7] Figure 4 shows FFS distributions by treatment strata. The stratum with the best outcome was alveolar/UDS stage 1 or group I, which had an outcome similar to that of patients treated on COG D9602 for low-risk patients with embryonal histology in which they received almost a year of VAC chemotherapy.[22]

In conclusion, this randomized study of VAC versus VAC/VTC did not show an improvement in outcome for patients with intermediate-risk RMS when topotecan was substituted for dactinomycin in half the cycles. The current intermediate-risk study is investigating irinotecan, another topoisomerase inhibitor, with even greater activity in preclinical models and in up-front phase II window studies as well as the role of early radiotherapy in all patients.[23-26]

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject

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